Epstein Barr–virus (EBV) associated T–cell clonopathy mimicking lymphomatous meningitis

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Sirs: Epstein Barr-virus (EBV) exhibits strong B-cell tropism. In chronic EBV-infection, T-cells may also be affected, which often expand monoclonally and then may progress into T-cell lymphoma [2, 3]. We describe a young female with EBV-associated T-cell clonopathy presenting twice with monoclonal infiltration of cranial and spinal nerve roots, which have not converged into lymphoma by now after seven years.

In 1997, the 20-year-old patient developed fever (≤ 40 °C), fatigue, hepatosplenomegaly and mild lymphadenopathy with pancytopenia (Hb 8.3 g/dl, platelets 80000/µl, neutrophils 500/µl), mildly elevated CRP (26 mg/l), increased gammaglobulins (22 g/l), thymidin-kinase (59.2 U/l), soluble interleukin-2 receptor (sIL-2r) (10696 U/ml) and neopterin (56.9ng/ml). A macrophage activation syndrome (characterized by elevated sIL-2r and neopterin) was suspected and a bone-marrow biopsy performed, revealing massive hemophagocytosis. The patient was splenectomized. Southern blots revealed monoclonal TCRβ-rearrangement with singular restriction bands identical in bone-marrow, blood and spleen, PCR singular TCRγ-amplifications identical in blood and spleen. Based on pediatric treatment schemes, aiming at macrophage inhibition, low-dose VP16-chemotherapy (2 × 150 mg/m^2) was initiated. Fever and inflammation markers declined.

Five weeks later, the patient developed fever, ear-pain and diplopia. Clinical examination revealed a mild meningism and right abducens nerve palsy. Three lumbal punctures showed mild pleocytosis (75/µl, reactive T-cells) and elevated protein (1.63 g/l). Blood EBV-VCA IgG/IgM and EBV-EBNA IgG titres were increased. Cranial MRI exhibited meningeal contrast-enhancement along cranial nerves suggestive of lymphomatous meningitis. Intrathecal chemotherapy with methotrexate (9 × 15 mg) and AraC (9 × 40 mg) was started, followed by dexamethasone. CSF cell-counts decreased to 2/µl, CSF protein to 0.49 g/l. Clinical symptoms and neurological abnormalities disappeared.

In 2002, hyposmia, hypoacusis and mild urinary disturbances were noted by the patient, followed by dizziness and gait disturbances three months later. On clinical examination, bilateral L3-S1 deficits with areflexia and positive Lasegue's sign were found. Blood examinations showed normal cell-counts and CRP, reduced gammaglobulins (1.5 g/l), increased sIL-2r (1359IU/ml) and neopterin (3.5 ng/ml), normal cyclin-D1 and positive EBV-PCR (125 DNA copies/ml). A mild CSF pleocytosis (36 cells/µl, reactive T-cells) with elevated CSF protein (2.6 g/l) and positive CSF EBV-PCR were found. Both the blood and CSF still exhibited monoclonal TCRγ-rearrangement with identical clones as six years before. MRI revealed contrast-enhancement with dural broadening around cranial and spinal nerve roots (Figure). In the absence of lymphoma cells in three lumbar puncture specimens, dexamethasone (4 × 8 mg) and intravenous immunoglobins (3 × 30 g) were started. Clinical symptoms rapidly improved. Today, fourteen months later, the polyradicular deficits have normalized. The patient complains about mild dizziness and (sensory) hearing difficulties.

In our patient, the recurrent cranial and spinal nerve root infiltrations reflect a steroid-responsive, EBV-related lymphoproliferative disorder. The absence of malignant cells in the blood and CSF, the negative tumour markers and clinical course allow the exclusion of the presence of a T-cell lymphoma. Neurological complications sometimes occur in acute and reactivated EBV, but rarely in chronic active EBV-infection [1]. Three patients with chronic active EBV-infection and encephalitis have been reported [1, 4, 5]. Two patients had fatal outcomes, all three patients exhibited brain parenchymal involvement on MRI. Thus, this is the first report of isolated meningoradicular infiltration in chronic active EBV-infection. In our patient, a gammaglobulin deficiency was detected during the second disease manifestation, whereas the first episode developed shortly after chemotherapy. Thus, immunodeficiency may have played a pathogenic role.

Monoclonal T-cell expansion following chronic EBV-infection is widely regarded as a guaranteed prelude to malignant lymphoma. In most cases, this is indeed clearly the case, although our patient shows that long-term survival is possible in a subset of patients. At present, our patient's long term prognosis remains unknown. In conclusion, meningeal monoclonal T-cell infiltration in the presence of chronic active EBV-infection should not mislead one to the diagnosis of T-cell lymphoma, unless a cytological diagnosis is

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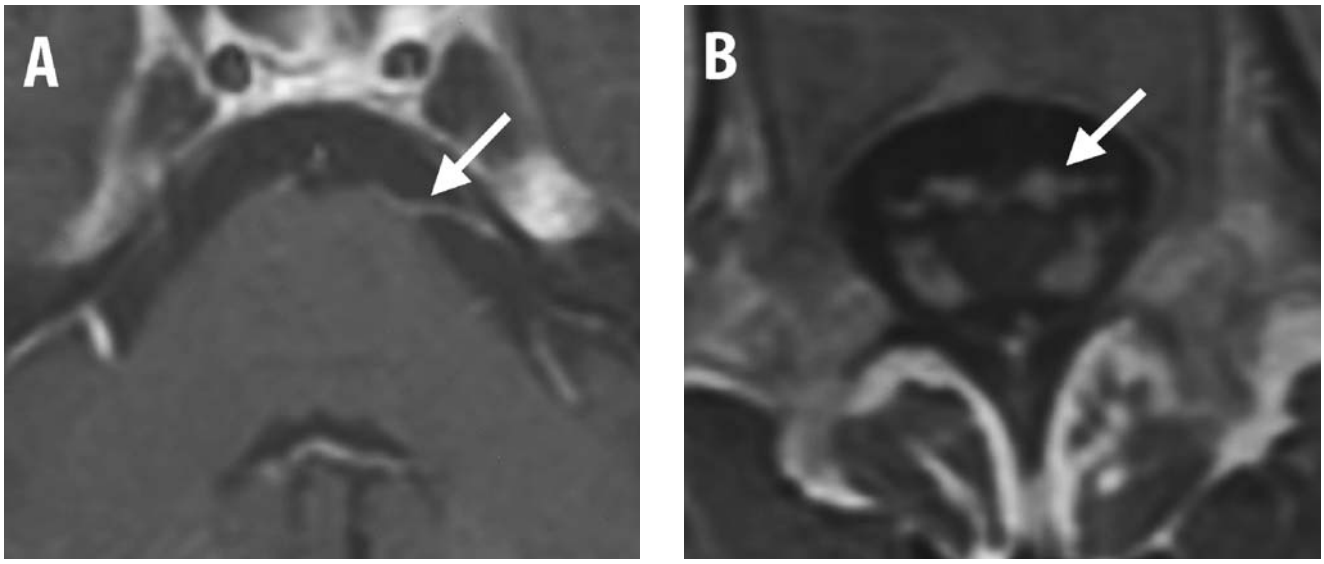

Fig. Gadolinium-enhanced T1-weighted MRI showing massive meningeal contrast enhancement (flashes) along cranial (**A**) and lumbar spinal (**B**) nerve roots

made. Clinical manifestations may well respond to steroids, allowing the avoidance of chemotherapy.

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